Pilot pharmacologic randomized controlled trial for psychogenic nonepileptic seizures

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ABSTRACT

Objective: There have been few treatment trials for psychogenic nonepileptic seizures (PNES). Some psychotherapies have been shown to improve PNES and comorbid symptom outcomes. We evaluated a pharmacologic intervention to test the hypothesis that sertraline would reduce PNES.

Methods: We conducted a pilot, double-blind, randomized, placebo-controlled trial in an academic medical hospital with epilepsy center outpatients. Subjects aged 18 to 65 years diagnosed with video-EEG–confirmed PNES were treated with flexible-dose sertraline or placebo over 12 weeks. Seizure calendars and symptom scales were charted prospectively. Secondary outcome measures included psychiatric symptom scales and psychosocial variables.

Results: Thirty-eight subjects enrolled, and 26 (68%) completed the trial. Thirty-three subjects with nonzero nonepileptic seizure rates at baseline were included in intent-to-treat analysis of the primary outcome. Subjects assigned to the sertraline arm experienced a 45% reduction in seizure rates from baseline to final visit ($p = 0.03$) vs an 8% increase in placebo ($p = 0.78$). Secondary outcome scales revealed no significant between-group differences in change scores from baseline to final visit, after adjustment for differences at baseline.

Conclusions: PNES were reduced in patients treated with a serotonin selective reuptake inhibitor, whereas those treated with placebo slightly increased. This study provides feasibility data for a larger-scale study.

Level of evidence: This study provides Class II evidence that flexible-dose sertraline up to a maximum dose of 200 mg is associated with a nonsignificant reduction in PNES rate compared with a placebo control arm (risk ratio 0.51, 95% confidence interval 0.25–1.05, $p = 0.29$), adjusting for differences at baseline. *Neurology*® 2010;75:1166–1173

GLOSSARY

AED = antiepileptic drug; **CI** = confidence interval; ***DSM-IV*** = *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*; **ES** = epileptic seizures; **ITT** = intent to treat; **PNES** = psychogenic nonepileptic seizures; **PTSD** = posttraumatic stress disorder; **QOL** = quality of life; **RCT** = randomized controlled trial; **RIH** = Rhode Island Hospital; **RR** = risk ratio; **SSRI** = serotonin selective reuptake inhibitor; **vEEG** = video-EEG.

Reports of pharmacologic therapy for psychogenic nonepileptic seizures (PNES) were first published at the turn of the 20th century[1] and have reappeared in later case reports[2]; however, no definitive randomized controlled trials (RCTs) have been completed to date.[3-6] Some medically unexplained symptoms (presumed psychogenic) have been shown to be responsive to pharmacologic interventions.[7-11] In addition to their established efficacy for treating depression and anxiety,[12] serotonin selective reuptake inhibitors (SSRIs) have shown promise in trials for conversion or somatoform disorders[11,13] and some personality disorders.[14] These frequently occurring comorbidities in patients with PNES[15] make SSRIs particularly attractive as a potential treatment for patients with PNES.

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Acknowledging the heterogeneity in the PNES population and the observed benefit of SSRIs in other somatoform disorders, we proposed a pharmacologic treatment with therapeutic breadth that addresses both comorbidities and PNES directly. Based on the high frequency of Axis I and II serotonergic-mediated symptoms in PNES (i.e., depression,[16] anxiety and impulsivity[17]), we initially hypothesized that treating the comorbidities in patients with PNES would reduce PNES. SSRIs are a reasonable choice to safely treat these conditions. Of the SSRIs, sertraline (Zoloft®; Pfizer, New York, NY) has the broadest US Food and Drug Administration indications and the fewest drug-drug interactions, a concern because many such patients with seizures also use antiepileptic drugs (AEDs). An open-label trial of flexible-dose sertraline in 8 patients with PNES for proof of concept was conducted preceding the current pilot RCT.[13]

The primary hypothesis of this pilot RCT was to assess the magnitude of seizure frequency reduction by treatment to inform a power analysis for a full-scale RCT. Secondary hypotheses were to identify potential predictors of treatment response.

METHODS

Standard protocol approvals, registrations, and patient consents. We received approval from the Rhode Island Hospital (RIH) Institutional Review Board, received written informed consent from all patients participating in the study at enrollment, and provided the ClinicalTrials.gov identifier: NCT00159965.

Patients and procedures. Patients were referred to the RIH neuropsychiatry/behavioral neurology clinic between July 2002 and June 2008, after being diagnosed with PNES. PNES diagnosis was established by capturing at least 1 of the patient's typical PNES on video-EEG (vEEG). The standard 10–20 electrode system was used and was recorded by cable, 16-channel telemetry, combined EEG and video recording. EKG was monitored. Data were collected in a standard fashion that included interictal samples and all recorded episodes. The combined vEEG recordings were reviewed by a board-certified epileptologist (A.S.B.).

The diagnosis of PNES was defined as stereotypic, motor manifestations (including the initiation or cessation of motor activity/staring), with or without change in level of consciousness, on vEEG with no recognizable buildup of rhythmic epileptiform (ictal) activity immediately before, during, or after the event. Patients, and family members, if present, were given the diagnosis in the RIH comprehensive epilepsy center in a standard format explaining the differences between epilepsy and PNES and their divergent treatments. Patients who were potential study candidates underwent neuropsychiatric examination and clinical screening by a board-certified neurologist and psychiatrist (W.C.L.).

Inclusion criteria were age between 18 and 65 years and vEEG diagnosis of PNES. Patients had to have experienced at least 1 event in the month before enrolling. Patients with only subjective sensory seizures without apparent loss of consciousness or behavioral arrest were excluded. Patients with mixed epileptic seizures (ES) and PNES who could clearly distinguish between their events were included (n = 2). Other exclusion criteria included using monoamine oxidase inhibitors or pimozide within 30 days before study, receiving optimized sertraline currently (≥100 mg daily for 3 weeks), presence of current psychosis, suicidality, or *DSM-IV* substance dependence diagnosis, inability to complete written surveys, pending litigation, or disability application. Participants currently taking an antidepressant were allowed to enroll, but all medication dosages were held constant during the trial. Participants currently receiving psychotherapy were allowed to enroll; however, those beginning new therapy were excluded.

After enrolling, patients documented their pre-enrollment PNES frequency for 2 weeks before enrollment and rated their psychosocial functioning and symptoms. Baseline measures from the 38 patients in this study were used in a larger cross-sectional study of quality of life (QOL) in PNES.[18] As part of the initial examination establishing PNES and the comorbid diagnoses, participants were also administered the Structured Clinical Interview for *DSM-IV* Axis I Disorders and Structured Interview for *DSM-IV* Personality Disorders by trained research interviewers. Additional historic and medical data were collected from chart review, patient query, and self-report surveys. Self-report and clinician symptoms scales were prospectively administered biweekly during the visits, with patients reporting symptoms for the 2 prior weeks.

Study design. Patients were treated in a double-blind, randomized, placebo-controlled trial. Patients were randomly assigned in blocks of 10, by a computer-generated schedule, in a 1:1 ratio to either the placebo or the sertraline group. Both patient and physician were blinded to treatment group. Allocation was concealed by having the RIH pharmacy generate and maintain the randomization schedule. Pharmacy prepared similar-appearing capsules of 25-, 50-, or 100-mg dosages of the medications. The blind was not broken until after the entire study was completed. Patients were followed up prospectively for 2 weeks without treatment to establish a baseline for measures. Beginning day 15, patients were started on either 25 mg sertraline or 25 mg placebo equivalent. The flexible-dosage design was that sertraline or placebo dose was increased in biweekly intervals to 50 mg, and then by 50-mg increments to a maximum of 200 mg daily, unless increase was limited by side effects. Subjects were seen in six 30-minute, biweekly sessions, according to a pharmacologic trial protocol[19] by a clinician with more than 10 years of experience in neurologic and psychiatric pharmacotherapy (W.C.L.). The session consisted of delineating subjects' PNES frequency and side effects, and adjusting medication dose. Missed appointments were made up during the same or following week.

Measures. Beginning at enrollment, patients recorded their PNES prospectively using a daily seizure calendar, which was aggregated into biweekly intervals. Collateral information from family informants was encouraged because some patients with ES and PNES may be unaware of their events. Secondary outcome measures are listed in table 1. A trained rater, blinded to treatment group, assessed symptom and psychosocial functioning scales. The Oxford Handicap Scale and Clinician Global

Table 1 Questionnaires used for secondary outcome measures

Subjective depression symptoms: Beck Depression Inventory II[28]
Objective depression symptoms: Modified Hamilton Rating Scale for Depression[29]
Anxiety/posttraumatic stress disorder symptoms: Davidson Trauma Scale[30]
Dissociative symptoms: Dissociative Experiences Scale[31]
Impulsivity: Barrett Impulsivity Scale[32]
Family functioning: Family Assessment Device[33,34]
Somatic symptoms: Symptom Checklist-90[35]
Patient symptoms and social functioning: Global Assessment of Functioning[36]
Disability: Oxford Handicapped Scale[37]
Psychosocial functioning: Longitudinal Interval Follow-up Evaluation–Range of Impaired Functioning Tool[38]
Coping techniques: Ways of Coping[39]
Quality of life: Quality of Life in Epilepsy-31[40]

Improvement Scale were assessed by a clinician blinded to treatment group.

Statistical methods. Data were analyzed using SAS for Windows 9.1.3 (SAS Institute, Inc., Cary, NC). Continuity-adjusted χ^2 was used to compare treatment groups on baseline categorical variables. Between-group differences in continuous variables at baseline were evaluated using the Student *t* test. Seizure counts were modeled using Poisson regression. The Poisson is a distribution on the positive integers appropriate for describing seizure counts; its sole parameter describes both its central tendency and its variance. The Poisson distribution can be approximated by the normal distribution when the event rate or sample size is high; therefore, count data can be modeled adequately using normal linear regression. However, for small sample sizes, Poisson regression is preferred. Mean seizure rate at final as the outcome and mean seizure count at baseline as an offset were used to estimate the within-group change in relative frequency of seizures through the course of the study. The resulting rate ratio was used as a measure of the treatment effect across the 2 study conditions. Patients with zero seizures in the baseline period were removed from this analysis because percentage improvement from baseline to follow-up could not be calculated for such subjects. A scale parameter was also included to adjust standard errors for overdispersion (variance greater than the mean). Analysis of covariance in which change scores from baseline to final visit were compared across study arms, after adjustment for differences at baseline, was used to estimate within-group changes on continuous secondary outcomes. Under an intent-to-treat (ITT) approach, subjects with missing data at the end of the study had their retrospectively reported baseline values carried forward to visit 6.

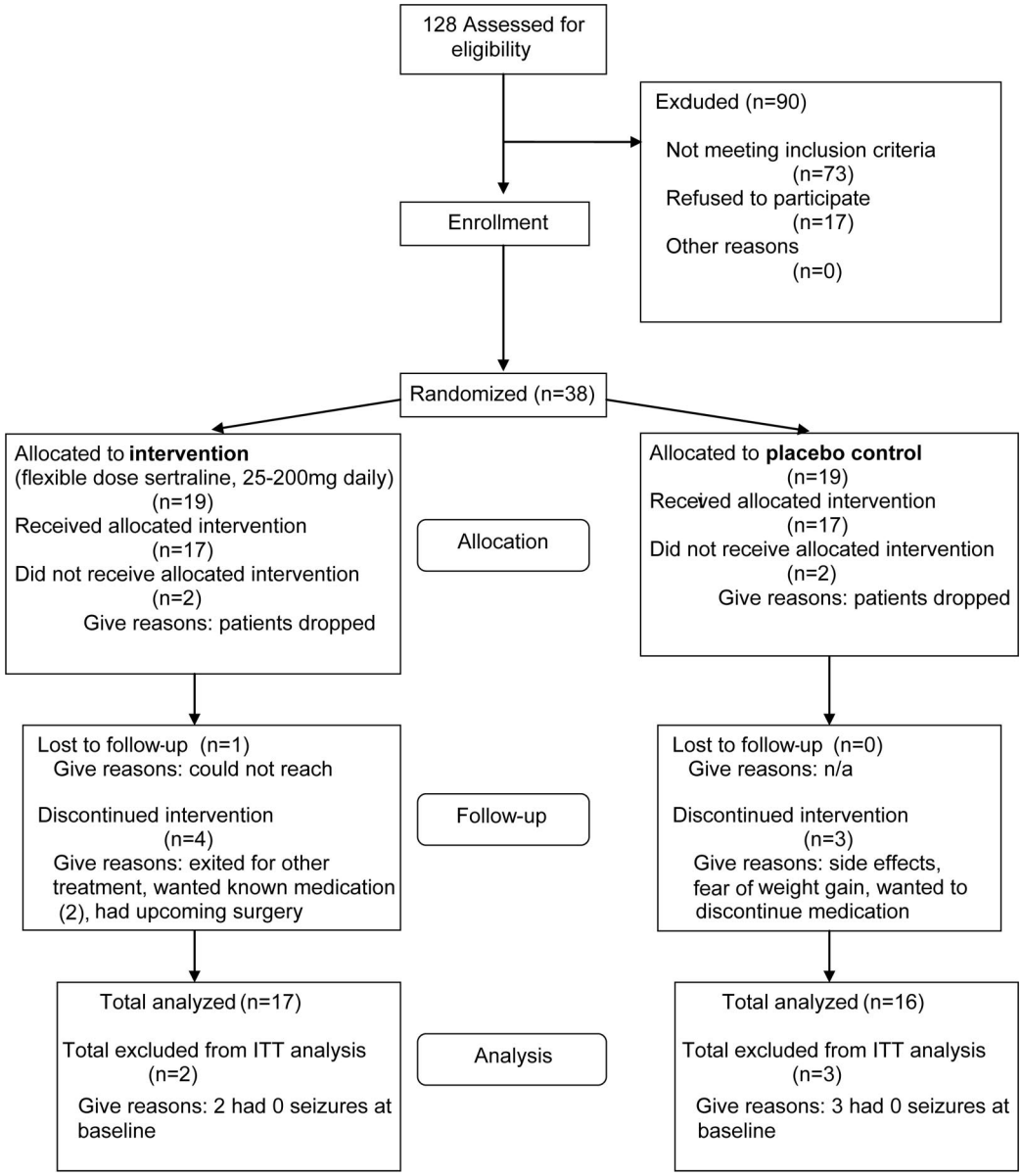
RESULTS Ninety of the 128 patients who were assessed for eligibility were excluded. Seventy-three did not meet inclusion criteria, and 17 were eligible but declined participation or were geographically unable to participate and did not enroll. Reasons for exclusions included using an optimized SSRI (n = 29), inability to differentiate events (n = 11), infrequent events (n = 9), no vEEG (n = 8), age (n = 7), and other exclusions (n = 9) (figure).

Sociodemographic data, comorbidities, and clinical factors were similar in both placebo and sertraline groups. Patients in the placebo arm reported slightly higher unemployment, anxiety and Axis II diagnoses, AED use, and a family history of seizures. Patients in the treatment group reported slightly higher frequency of mood diagnoses, trauma history, prior treatment with antidepressants or with psychotherapy, and seizures; however, none of the differences between the 2 groups were significant (table 2). Similarly, baseline measures in the placebo group revealed higher baseline mean self-reported depression scores, impulsive symptoms, and overall symptoms, whereas the treatment group reported higher baseline mean trauma symptoms and dissociative symptoms; none of these differences were significant (table 3).

Of the 38 participants who enrolled, 26 subjects provided end-of-study data (68% study completion rate) (table 3). Sixteen of the 19 who received active drug tolerated a dose of at least 100 mg, with 10 patients tolerating up to the maximum of 200 mg daily. There were no severe adverse events. Thirty-three subjects were included in the ITT analyses for the primary outcome. Subjects excluded from the Poisson regression models consisted of 5 patients with a retrospectively reported biweekly baseline rate of zero seizures, because the outcome of interest (relative change in PNES rates from baseline to end of study) could not be calculated for such subjects.

Primary analysis: Treatment effect on seizure frequency. ***Relative change in seizure rates.*** There was no difference between treatment groups (risk ratio [RR] 0.51, 95% confidence interval [CI] 0.25–1.05, $p = 0.29$). However, further analyses were conducted using an overdispersed Poisson regression model to estimate relative change in biweekly seizure rates from baseline to study end, separately, by treatment group. These analyses indicated that patients in the sertraline arm manifested a 45% decline in biweekly seizure rates over the 12-week course of the intervention from 22.24 to 12.18 (ratio 0.55, 95% CI 0.32–0.93, $p = 0.03$). In contrast, control subjects experienced an 8% increase in biweekly seizure rates from 13.38 to 14.38 (ratio 1.08, 95% CI 0.65–1.77, $p = 0.78$). Using the ratio of these 2 ratios (RR) as a summary measure of treatment effectiveness, our study provides suggestive evidence that pharmacologic treatment reduced seizure rates in the sertraline arm relative to a placebo control arm, adjusting for differences in seizure rates at baseline. Table 4 presents the raw mean and median seizure counts for all visits before exit. Cross-sectional Poisson regressions revealed no between-condition differ-

Figure CONSORT flowchart: Psychogenic nonepileptic seizures pilot pharmacologic randomized controlled trial



CONSORT = Consolidated Standards of Reporting Trials; ITT = intent-to-treat.

ences significant at $\alpha = 0.05$ at any of the intermediate time points.

Fifty percent change in seizure rates. Among subjects with nonzero retrospectively reported baseline seizure rates, 8 of 17 patients in the sertraline arm reported a 50% or greater reduction in the seizure frequency by their final session, compared with 3 of 16 patients in the placebo arm (ITT rates of 47.1% vs 18.8%, $p = 0.18$), resulting in a number needed to treat of 3.53. Of these responders, 6 patients in the sertraline group reported complete cessation, vs a single patient in the placebo group (ITT rates of 35.3% vs 6.3%, $p = 0.08$).

Among patients with nonzero baseline rates who provided information at study end, sertraline subjects with Axis II disorders (n = 5) reported higher baseline biweekly seizure rates than those without Axis II diagnoses (n = 9). In the placebo group, there were no significant differences in baseline seizure rates between patients with (n = 11) and without (n = 3) Axis II disorders.

Secondary outcomes. Mean scores on secondary outcome scales assessing depression, anxiety, impulsivity, somatic symptoms, QOL scores, and psychosocial functioning did not reveal between-arm differences in change scores from baseline to final session, after adjustment for differences at baseline (all $p > .05$) (table 3).

Table 2 Patient baseline characteristics for PNES pharmacologic pilot randomized, placebo-controlled trial (N = 38)[a,b]

	Placebo (n=19)		Sertraline (n =19)	
	Mean (SD)	n (%)	Mean (SD)	n (%)
Sociodemographic factors (self-reported)				
Age, y	34.4 (12.6)		38 (13.9)	
Age at PNES onset, y	28.4 (15.2)		33.5 (16.2)	
Female sex		13 (68.4)		16 (84.2)
Education, y	12.7 (2)		13.9 (2.5)	
Unemployed currently		14 (73.7)		11 (57.9)
Receiving disability currently		7 (36.8)		6 (31.6)
Married currently		8 (42.1)		10 (52.6)
Driving currently		5 (26.3)		7 (38.9)
Clinical diagnosis[c] (made by MD and SCID)				
Mood disorders[c]		10 (52.6)		13 (68.4)
Anxiety disorders[c]		17 (89.5)		16 (84.2)
Axis II disorder		12 (63.2)		8 (42.1)
Impulsivity (cluster B personality or traits)		5 (26.3)		5 (26.3)
Somatoform disorders[c] (other than PNES)		8 (42.1)		5 (26.3)
Clinical factors (from history at baseline)				
History of trauma/abuse		14 (73.7)		17 (89.5)
Previous psychotherapy		10 (52.6)		12 (63.2)
Treated with psychotropic medications (past and current)		15 (79)		17 (89.5)
Benzodiazepines		6 (31.6)		5 (26.3)
Antidepressants		7 (36.8)		12 (63.2)
Antipsychotics		1 (5.3)		2 (10.5)
Using AEDs at baseline		12 (63.2)		6 (31.6)
Average total number of lifetime AEDs	2.8 (3)		2 (2.1)	
Average time from PNES onset to diagnosis, y	4.6 (6.3)		3.7 (5.8)	
Seizure frequency (2 wk before enrollment)	11.3 (12.1)		19.9 (43.5)	
Abnormal neurologic examination result at enrollment		13 (68.4)		11 (57.9)
Abnormal MRI of the brain (past or at enrollment)		10 (52.6)		6 (31.6)
30-min EEG tracing				
Interictal epileptiform activity		7 (36.8)		4 (21.1)
Slowing only abnormality		2 (10.5)		4 (21.1)
Biological family history of seizures		11 (57.9)		5 (27.8)
History of head injury		7 (36.8)		8 (42.1)

Abbreviations: AED = antiepileptic drug; PNES = psychogenic nonepileptic seizures; SCID = Structured Clinical Interview for *DSM-IV* Axis I Disorders.
[a] Patient medical history obtained by interview and record review.
[b] All between-group comparisons $p > 0.05$ (not significant).
[c] Not mutually exclusive.

DISCUSSION In this pilot RCT, we assessed SSRI treatment to reduce seizure frequency in PNES. The trial was not powered for establishing treatment efficacy; rather, it was conducted to establish an effect size for a pharmacologic intervention and to demonstrate feasibility of conducting a future multicenter RCT for PNES. Given the small, pilot nature of this trial, it is not surprising that no significant differences were found in seizure rates between sertraline and placebo groups. Nonetheless, patients in the sertraline arm manifested a significant 45% decline in biweekly seizure rates vs control subjects, who experienced a nonsignificant 8% increase, suggesting that subjects assigned to the sertraline arm received some benefit relative to placebo. This pilot trial can neither substantiate nor refute the utility of SSRI treatment in patients with PNES.

Analysis of secondary outcome measures including psychiatric symptoms, QOL, family functioning, and psychosocial functioning did not reveal significant differences between the treatment and placebo groups. This finding differs markedly from that in a trial of cognitive behavioral therapy for PNES conducted in parallel with this study that showed not only reduced PNES frequency, but also improved symptoms of depression and anxiety, QOL scales, and family functioning.[20] The lack of significant improvement in secondary outcome measures in this pilot pharmacologic trial provides indirect evidence that the pharmacologic trial may not have been "contaminated" with psychotherapy, a potential concern for pharmacologic trials.[19]

The population enrolled in our trial was reflective of this disorder's complexity, as noted in clinical practice and reported in the literature. Sociodemographic characteristics of the 38 participants who enrolled and completed baseline measures are consistent with current PNES literature. Neurologically, a number of patients with PNES 1) have neuroimaging abnormalities of uncertain relevance, 2) have interictal EEG abnormalities despite no epileptiform abnormalities during their seizure, and 3) have abnormal neurologic examination results despite the absence of a "focal lesion" causing their events. Psychiatrically, patients with PNES are a heterogeneous population having at least 1 comorbid condition, including depression, anxiety, posttraumatic stress disorder (PTSD), or a personality disorder.[15] In this study, most of the participants had more than 1 Axis I disorder accompanying their diagnosis of PNES. More than half had a mood, anxiety, or personality disorder. Given that SSRIs are the treatment of choice for the comorbidities, and to maximize generalizability to PNES populations seen in hospitals and clinics, we included patients with anxiety, mood, or personality disorder or a combination of the disorders. If current psychiatric clinical trial exclusion criteria were applied to "real-world" outpatients, the majority of patients seen in practice, up to 90%, would be excluded from RCTs, thus limiting generalizabil-

Table 3 Assessment ratings at baseline and exit in psychogenic nonepileptic seizures pharmacotherapy pilot randomized controlled trial[a,b]

		Placebo		Sertraline	
Scale	Cutoff[c]	Baseline (n = 19), mean (SD)	Exit (n = 14), mean (SD)	Baseline (n = 19), mean (SD)	Exit (n = 12), mean (SD)
Modified Hamilton Depression Scale	<7	16.8 (8.8)	13.3 (8.4)	17.8 (21.0)	11.6 (9.0)
Beck Depression Inventory II	<14	22.1 (13.9)	17.0 (13.3)	16.7 (13.0)	11.7 (11.5)
Davidson Trauma Scale	<17	48.1 (40.0)	43.4 (40.0)	52.5 (31.6)	40.3 (36.9)
Barrett Impulsivity Scale	<70	72.6 (17.8)	66.2 (15.9)	57.8 (16.5)	64.9 (13.2)
Dissociative Experiences Scale	<5	17.4 (11.0)	12.1 (12.2)	21.0 (19.7)	8.5 (13.2)
Symptom Checklist-90	<85	109.4 (70.9)	91.4 (77.2)	84.9 (73.3)	78.9 (67.2)
Global Assessment of Functioning*	>80	49.1 (7.1)	52.0 (7.9)	53.3 (10.3)	56.8 (11.0)
Oxford Handicap Scale	<2	3.4 (0.7)	2.6 (1.2)	3.1 (0.8)	2.3 (1.3)
Clinical Global Impressions–Improvement	1	—	3.5 (1.6)	—	2.9 (1.4)
Clinical Global Impressions–Severity	1	5.1 (0.6)	3.9 (0.9)	4.9 (0.8)	3.3 (1.6)
Quality of Life in Epilepsy-31*	>63	38.2 (19.0)	46.9 (24.0)	48.4 (20.7)	56.7 (25.1)
Family Assessment Device–General Functioning Subscale Score	<2.00	2.0 (0.5)	2.2 (0.5)	2.0 (0.7)	2.0 (0.6)
LIFE-RIFT (QOL measure)	<9	13.9 (3.8)	13.8 (3.3)	11.8 (3.6)	11.8 (4.8)
Ways of Coping[d]		Self-controlling and seeking social support	Self-controlling and positive reappraisal	Self-controlling	Self-controlling and positive reappraisal

Abbreviations: LIFE-RIFT = Longitudinal Interval Follow-up Evaluation–Range of Impaired Functioning Tool; QOL = quality of life.

[a] Analysis of covariance, comparing change from baseline to exit across conditions, covarying for baseline; return to baseline imputed for missing values at exit; no between-condition p values were significant at $\alpha = 0.05$.

[b] For all assessments, except those marked with an asterisk, a higher score indicates a worse condition.

[c] Cutoff/anchor scores in controls and healthy subjects from the literature.

[d] Coping method most used.

ity.[21,22] Future studies may benefit from stratifying groups on the presence of personality disorders.

None of the prior PNES treatment studies approached Class I evidence.[3,4,23-25] This pilot study misses only 1 Class I criterion (68% enrollment, vs criterion d, at least 80% completion).[26] Although results did not attain significance at the customary 5% level, the present study provides Class II evidence that flexible-dose sertraline up to a maximum dose of 200 mg is associated with a nonsignificant reduction in PNES rate compared with a placebo control arm (RR 0.51, 95% CI 0.25–1.05, $p = 0.29$), adjusting for differences at baseline. The study also provides preliminary evidence of a serotonergic-mediated intervention directly on PNES, because seizure reduction in the sertraline group was not accompanied by a mean reduction in symptoms in common comorbidities of depression or PTSD. Based on this study, we modified our initial hypothesis that treating comorbidities may reduce PNES. SSRIs may have a direct effect on PNES. In fact, other studies have recently reported a direct effect of SSRIs on somatoform disorders, independent of mood and anxiety symptoms.[8,27] That the treatment group began showing seizure improvement at lower doses of the SSRI may indicate that somatoform disorders may have a lower serotonergic response threshold than mood and anxiety disorders. This response was not observed in the placebo group, arguing against an early placebo response in the treatment group.

Half of the patients had received an antidepressant before enrollment. Despite using antidepres-

Table 4 Mean and median psychogenic nonepileptic seizure frequency as a function of visit[a]

	Placebo (n = 19)		Sertraline (n = 19)	
2-wk count at:	Mean (SD)	Median	Mean (SD)	Median
Baseline (retrospective 2 wk prior)	11.3 (12.1)	6.0	19.9 (43.5)	5.0
Week 2 (prospectively collected from days 1–14)	8.9 (8.5)	6.0	17.8 (37.7)	3.0
Week 4	10.3 (10.6)	5.0	16.1 (31.5)	2.0
Week 6	10.9 (16.4)	3.0	13.1 (31.5)	1.0
Week 8	12.1 (17.4)	3.0	12.1 (24.4)	1.0
Week 10	11.7 (12.4)	7.0	18.7 (30.7)	2.5
Week 12	11.6 (14.0)	6.0	11.7 (20.3)	0.0

[a] Raw means and medians provided with standard deviation of biweekly seizure count. Overdispersed Poisson regression with return to baseline imputed for missing values at follow-up visit; no between-condition p values were significant at $\alpha = 0.05$.

sants at some point in the past, they did not have symptomatic improvement in seizures during their pre-enrollment regimen, suggesting that optimizing the dose of antidepressant may be an important treatment component. Also, patients who do not respond to one SSRI may respond to another. The patients taking AEDs at baseline were prescribed the drug not only for seizures, once thought epilepsy, but also for other AED-responsive conditions, including migraine prophylaxis (n = 4), mood disorder (n = 3), pain (n = 4), and comorbid epilepsy (n = 2). One could argue that ongoing AED use can in some cases reflect lack of confidence in the diagnosis of PNES, and that may influence outcomes. However, the explanation given to the participants was clear that 1) AEDs do not treat PNES, and 2) if they continued on their AED for other indications, it was not being used for seizure reduction in their treatment. The patients understood the indication for their AEDs, and with this clarification, we hoped to mitigate any reduction in confidence in the PNES diagnosis.

The major limitation of this pilot study's conclusions is sample size. A full-scale RCT is needed to establish efficacy for a pharmacologic intervention for PNES. The future full-scale trial will need to adjust for potential dropouts, which largely occurred in this trial because of the patients' concern that they would receive the placebo, despite the equipoise that exists for PNES treatments. Although the evenly dispersed baseline slight differences among the 2 groups could have contributed to the apparent treatment difference, our analyses confirmed that there were no significant differences among any of the factors related to illness severity. One of the major strengths of this study was that all patients had vEEG-documented PNES. However, excluding patients who did not have vEEG may present a potential sampling bias.

The trial provides feasibility and patient tolerability for a pharmacologic intervention for PNES. The potential influence of patient characteristics was also highlighted in this pilot study. Future studies on response durability, documenting treatment effect duration, need to be conducted. A multicenter RCT is being designed to address the efficacy of treatments for PNES.

AUTHOR CONTRIBUTIONS

Statistical analyses were conducted by Drs. George D. Papandonatos and Jason T. Machan.

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DISCLOSURE

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